75-Day Premarket Notification for A New Dietary Ingredient

In compliance with the requirement of 21 CFR§190.6, I am submitting a premarket notification of my intent to distribute a dietary selenium supplement consisting of a new dietary ingredient, methylseleninic acid.

Submitted by:

Edgar N. Drake, Ph.D., President
Rocky Mountain Selenium, Inc.
2101 Ridge Road
Estes Park, CO 80517
Phone: 970-586-1946
Fax: 970-577-1064

ORB/FDA

New Dietary Ingredient: methylseleninic acid

Proposed Dietary Supplement:

The product will consist of an aqueous solution containing 1770 micrograms of methylseleninic acid per milliliter (1100 micrograms selenium per milliliter) contained in a dropper bottle that dispenses 22 drops per milliliter such that each drop provides 50 micrograms of selenium in the form of methylseleninic acid.

Conditions of Product Use

The label will contain the following instructions for use:

"DIRECTIONS FOR USE: This product is for adults only. Take four drops daily as a dietary supplement. Do not exceed recommended dosage. This product is not intended to diagnose, treat, cure or prevent any disease".

KEEP OUT OF REACH OF CHILDREN

Evidence of Safety

It is now well recognized that the toxicity of selenium depends upon the chemical form rather the element *per se*. Regardless of the dietary form ingested, selenium is converted to hydrogen selenide, which is used as starting material for the biosynthesis of the essential selenoproteins (1). Once selenoprotein concentration requirements are satisfied, excess hydrogen selenide is methylated sequentially to methylselenol, dimethylselenide, and trimethylselenonium ion for excretion (2). Under most circumstances, virtually all

excess selenium is monomethylated producing methylselenol for urinary excretion. As progressively larger amounts of selenium are ingested, volatile dimethylselenide is produced for exhalation, and eventually trimethylselenonium ion, a second urinary metabolite, is produced to provide a third detoxification pathway (2).

Much of the interest in dietary selenium supplementation has arisen from studies demonstrating that selenium exhibits potent anticarcinogenic activity at supranutritional levels (i.e. 2 to 5 ppm dietary selenium) of intake (3-5). Although sodium selenite has been shown to be a more effective anticarcinogen than most other chemical forms of selenium (6-8) and has been used in the United States as a dietary selenium supplement for at least two decades, concerns about its potential toxicity have energized the search for other selenium compounds that are equally effective but less toxic. Sodium selenite supplementation has been shown to produce single-strand breaks in the DNA of some cancer cells (9) so that, in sufficiently large doses, the potential for similar genotoxicity in normal cells exists.

In 1992, A.C. Wilson, et al. (10) reported that selenobetaine and selenobetaine methyl ester, which are immediate precursors of the methylated excretory forms methylselenol and dimethylselenide, respectively, reduce the long-term growth potential (colony-forming ability) of mouse L1210 leukemia cells without affecting DNA integrity. The authors conclude: "These observations indicate that it is possible to maintain high intracellular levels of selenium, by exposure to methylated selenocompounds, without affecting DNA integrity".

The monomethyl selenium compounds methylseleninic acid and Se-methyl-L-selenocysteine, both immediate precursors of methlyselenol, have been studied to determine their tendencies to damage DNA and their abilities to replenish thioredoxin reductase activities in selenium-depleted cells (11). Neither compound produced measurable amounts of alkaline-labile DNA damage, and both showed adequate ability to replete thioredoxin reductase activity. Tissue levels of Se-methyl-L-selenocysteine were slightly higher that those of methylseleninic acid, presumably due to the more facile conversion of methylseleninic acid into methylselenol.

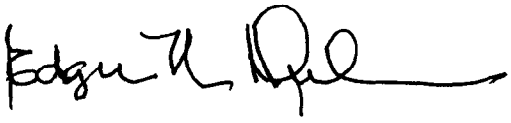
Recently, R. Gopalakrishna and U. Gundimeda (12) have shown that volatile methylselenol reacts with fatty acid hydroperoxides to produce non-volatile methylseleninic acid that ultimately reacts with thiol groups (e.g. on the four cysteine residues in the α and β isomers of protein kinase C) to regenerate methylselenol. Methylselenol was shown to have no direct effect on protein kinase C activity, but the methylseleninic acid produced by methylselenol selectively inactivates protein kinase C. Thus, methylseleninic acid is actually responsible for the protein kinase C inactivation heretofore attributed to methylselenol.

H. E. Ganther and C. Ip (13) have compared liver thioredoxin reductase activities of rats fed supranutritional amounts (2 µg Se/g diet) of Se-methyl-L-selenocysteine and methylseleninic acid with those fed a basal diet containing 0.1 µg Se/g diet (as sodium selenite). Liver thioredoxin reductase activities of rats fed supranutritional doses of either Se-methyl-L-selenocysteine or methylseleninic acid for periods of 3,6,10, or 22 weeks were indistinguishable from those of rats on basal selenium diets for the same time periods. In contrast, direct addition of 50 µmol. of dimethyldiselenide or dimethyl selenylsulfide per liter to liver extracts demonstrated significant toxicity by inhibiting thioredoxin reductase activity by approximately 60%. Since thioredoxin is involved in many cellular processes, thioredoxin reductase is likely to be an important regulatory protein for both normal and transformed cells.

In view of the fact that FDA has determined that a 200-µg Se/day dose of Se-methyl-L-selenocysteine is sufficiently safe for use in dietary supplements and that the toxicities of methylseleninic acid and Se-methyl-L-selenocysteine are virtually identical, I am hopeful that the same daily dose of methylseleninic acid will also be considered acceptable for the same application.

I respectfully request that all information contained in this submission be treated as confidential.

Very truly yours,



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